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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/827,133	ALLEN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11 and 15-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11,15-23,25 and 26* is/are rejected.

7)☒ Claim(s) *24 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/23/05, 11/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 11/9/2005, in which claims 5, 12-14, 28 and 29 were canceled; and claims 1, 2, 4, 6, 7, 9-11, 15, 17-19, 21 and 24 were amended. Currently, claims 1-4, 6-11 and 15-27 are pending and under consideration. Applicants' arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Receipt of information disclosure statements, filed on 6/23/2005 and 11/9/2005, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

Claim Objections

Claims 24 and 27 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims 24 and 27 have not been further treated on the merits. This objection was made in the Office action mailed 6/28/2005.

Response to Arguments - Claim Objections

Applicant's arguments filed 11/9/2005 have been fully considered but they are not persuasive. The response asserts that claims 24 and 27 have been amended to remove the improper multiple dependency. This is not found persuasive. Claim 24 depends from claim 22 and claim 7. Claim 27 depends from claim 25 and claim 15. Multiple dependent claims should refer to other claims in the alternative only. See MPEP § 608.01(n). The claim dependencies of claims 24 and 27 are not phrased in the alternative.

For these reasons, and the reasons made of record in the previous office actions, the objection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claim 4 is drawn to a nucleic acid construct comprising at least one modified protein selected from the group consisting of: a modified LuxA and a modified LuxB, further

comprising LuxC, LuxD, and LuxE, where the proteins are all proteins necessary for production of bioluminescence without addition of an exogenous substrate.

The specification teaches that the LucCDABE operon contains five genes necessary for self-sustained bioluminescence in bacteria: LuxAB is a luciferase, which catalyzes the light-producing reaction; LuxCE is a multi-component enzyme that converts myristic acid to a fatty aldehyde substrate for the light-producing reaction; and LuxD is a transferase that assists LuxCE (e.g. paragraph bridging pages 5-6). The specification teaches nucleic acid constructs comprising *luxA* and *luxB* genes in addition to *luxC*, *luxD*, and *luxE* genes (e.g. page 16, lines 22-27). Claim 4 reads on embodiments where the nucleic acid construct comprises *luxA*, *luxC*, *luxD*, and *luxE* genes, or a construct comprising *luxB*, *luxC*, *luxD*, and *luxE* genes. These combinations are not supported by the specification, claims or drawings as originally filed in that the specification teaches that both *luxA* and *luxB* are required in addition to the *luxC*, *luxD* and *luxE* genes for all proteins necessary for production of bioluminescence without addition of an exogenous substrate. The response does not point to portions of the specification, claims or drawings as originally filed as support for the amendment of claim 4.

Therefore, claim 4 represents a departure from the specification, claims and drawings as originally filed.

Claims 1-4, 6-11, 15-23 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified nucleic acid construct comprising a gene cassette encoding (1) a modified LuxA comprising a carboxy-terminal sequence selected from the group consisting of SEQ ID NOS: 8, 9 and 10, wherein the half-life of the modified

LuxA protein when expressed in an *E. coli* cell is shorter than the half-life of the wild-type form of the protein when expressed in the *E. coli* cell and (2) a modified LuxB comprising the PEST-rich 178 amino acid carboxy-terminal sequence of G1 cyclin Cln2, wherein the half-life of the modified LuxB protein when expressed in a yeast cell is shorter than the half-life of the wild-type form of the protein when expressed in the yeast cell does not reasonably provide enablement for any other modifications of LuxA or LuxB that result in a decrease in half-life in any type of cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a new rejection necessitated by Applicants' amendment of the claims in the response filed on 11/9/2005.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to or encompass a purified nucleic acid construct comprising a gene cassette encoding at least one modified protein selected from the group consisting of a modified LuxA and a modified LuxB, wherein the half-life of the modified protein when expressed in a cell is shorter than the half-life of the wild-type form of the protein when expressed in the cell. The modified Lux protein may be derived from a bacterium selected from the group consisting of *Photorhabdus luminescens, Vibrio fisheri* and *Vibrio harveyi*. The dependent claims limit the modifications to a protein associated with a proteolytic pathway, to a

protein associated with a tail-specific protease, to a peptide comprising a sequence selected from the group consisting of SEQ ID NO: 8, 9 or 10, to a protein associated with a ubiquitin-proteosome pathway, to a protein associated with SCF(GRR1), to a protein comprising a PEST rich sequence, or to the terminal sequence of G1 cyclin Cln2. Further, the claims encompass prokaryotic cells and eukaryotic cells, including yeast and mammalian cells, comprising the nucleic acid construct. Thus, the modifications of LuxA and LuxB must be capable of decreasing the half-life of the protein in any prokaryotic or eukaryotic cell.

Breadth of the claims: The claims are broad in that they encompass any modification of LuxA and/or LuxB that decreases the half-life of the proteins in any type of cell. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches that the products of the LuxAB genes encode a heterodimeric bioluminescent catalyzing enzyme and have been isolated from several bioluminescent bacteria including *Photorhabdus luminescens, Vibrio fisheri* and *Vibrio harveyi* (e.g. page 2, lines 3-10). The specification envisions modifications of LuxA and LuxB to allow rapid degradation via cellular proteolytic pathways, such as by tail-specific proteases in bacterial cells and by a ubiquitin-proteosome pathway in eukaryotic cells (e.g. page 3, lines 1-23; paragraph bridging pages 9-10).

The specification teaches the construction of the following plasmids: (1) pAaavB, which contains the luxA gene modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYAAV (SEQ ID NO: 8), and the wild type luxB, (2) pAlaaB, which contains the luxA gene modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYALAA (SEQ ID NO: 9), and the wild type luxB, (3) pAasvB, which

contains the luxA gene modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYAASV (SEQ ID NO: 10), and the wild type LuxB, (4) pABaav, which contains the luxB gene modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYAAAV (SEQ ID NO: 8), and the wild type LuxA, (5) pAaavBaav, which contains the luxA and luxB genes modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYÃAAV (SEQ ID NO: 8) (e.g. pages 13-14). To determine the effect of the carboxy-terminal peptides on the half-life of the LuxAB luciferase protein, the plasmids were transformed into *E. coli*. The plasmid pABaav did not result in a decrease in half-life (e.g. page 15, lines 16-19). The specification teaches that modifications of the luxA gene with the carboxy-terminal peptides decreased the half-life, whereas modifications of luxB had no effect (e.g. pages 15-16).

The specification teaches the construction of luxAcln and luxBcln, which contain the PEST-rich 178 amino acid carboxy-terminus of the G1 cyclin Cln2 (e.g. page 16, lines 15-21). The specification teaches that the luxAcln construct did not show a significant rate of decline in bioluminescence in yeast cells, whereas the luxBcln construct had a decreased half-life in yeast cells.

Thus, the specification teaches that luxA protein comprising a peptide selected from the group consisting of SEQ ID NOS: 8, 9 and 10 has a decreased half-life in *E. coli*, and a luxB protein comprising the PEST-rich 178 amino acids of G1 cyclin Cln2 has a decreased half-life in yeast cells, relative to the wild-type proteins in the same cell type.

Predictability and state of the art: As evidenced by the examples taught in the instant specification, the nature of the invention is unpredictable. For example, the addition of the

peptide of SEQ ID NO: 8 to luxA results in a decreased half-life of the protein relative to wild-type luxA, whereas the same modification to luxB has no effect. Modification of LuxB to include the PEST-rich 178 amino acid carboxy-terminus of G1 cyclin Cln2 results in a decreased half-life relative to wild-type luxB, whereas the same modification to luxA has no effect. Thus, the modification of luxA and/or luxB to decrease the half-life is unpredictable.

In the response filed 11/9/2005, Applicant acknowledges that the nature of the invention is "notoriously unpredictable" (e.g. page 12). As evidence of the unpredictable nature of the invention, the response points to the working of the examples of the specification, which are discussed above and on page 12 of the response. Further, the response states, "Adding an exogenous peptide sequence to LuxA or LuxB could have any number of consequences that could result in failure of the component to function." See the second paragraph on page 12 of the response.

The half-life of a protein in one cell type does not predict the half-life of a protein in another cell type. Andersen et al (Applied and Environmental Microbiology, Vol. 64, No. 6, pages 2240-2246, of record) teach the addition of a nucleic acid encoding a peptide of instant SEQ ID NO: 8, 9 or 10 to green fluorescent protein (Gfp) (e.g. page 2240, paragraph bridging columns; page 2243, Construction of unstable Gfp variants; page 2241, Plasmids; Table 1). Andersen et al state, "the half-life estimates obtained in the experiments presented are not to be taken as absolute, fixed values. The protease reaction resulting in degradation of Gfp may be dependent on strains, growth conditions, specific features of the surroundings, competing targets in the cell, etc." (see the paragraph bridging pages 2244-2245). Thus, the effect of a protein

modification in one cell type or in an *in vitro* assay does not predict the effect in another cell type.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use any nucleic acid construct comprising a modified LuxA or modified LuxB, wherein the half-life of the modified protein when expressed in a cell is shorter than the half-life of the wild-type protein. In order to carry out the claimed invention, one of skill in the art would have to identify a representative number of protein modifications that result in a decreased half-life in a particular cell type. Given the unpredictable nature of the invention, this would require a lot of trial and error experimentation with the effective reduction to practice of one species not providing any guarantee of success for other related species.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1-4, 6-11, 15-23 and 25-26 are not considered to be fully enabled by the instant specification.

Response to Arguments - 35 USC § 112

The rejection of claims 19-23, 25 and 26 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been withdrawn in view of Applicant's amendment.

Response to Arguments - 35 USC § 102

The rejection of claims 1, 2, 7, 15, 17, 19-23, 25, 26, 28 and 29 under 35 U.S.C. 102(b) as being anticipated by Leclerc et al has been withdrawn in view of Applicant's amendment.

Response to Arguments - 35 USC § 103

Applicant's arguments, see pages 9-13, filed 11/9/2005, with respect to the rejection(s) of claim(s) 1-14, 19-24 and 27-29 under 35 USC 103 as being unpatentable over Andersen et al in view of Hakkila et al have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the unpredictability of LuxA and LuxB modification.

The rejection of claims 1, 2, 7, 15-21, 25, 26, 28 and 29 under 35 USC 103 as being unpatentable over Vieties et al in view of Mateus et al has been withdrawn in view of Applicant's amendment.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Jennifer Dunston
Examiner
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